

WHAT IS CLAIMED:

1. A method of treating pain, inflammation or an inflammation mediated disorder, the method comprising:

(a) diagnosing a subject in need of treatment for pain, inflammation or an inflammation mediated disorder; and

5 (b) administering to the subject a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a potassium ion channel modulator or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

2. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC₅₀ to COX-2 IC₅₀ not less than about 50.

3. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC₅₀ to COX-2 IC₅₀ not less than about 100.

4. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, meloxicam, parecoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid, (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

5. The method of claim 1 wherein the potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride, 5 iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide, nateglinide, repaglinide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

6. The method of claim 4 wherein the potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride, iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide, nateglinide, repaglinide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

7. A method of treating pain, inflammation or an inflammation mediated disorder, the method comprising:

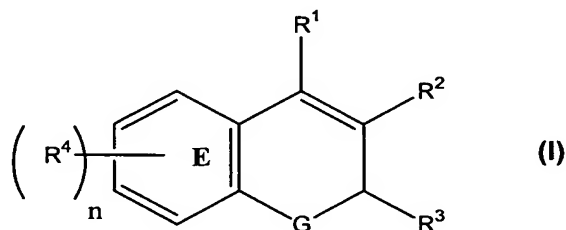
(a) diagnosing a subject in need of treatment for pain, inflammation or an inflammation mediated disorder; and

(b) administering to the subject a potassium ion channel modulator or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a chromene compound, the chromene compound comprising a benzothiopyran, a dihydroquinoline or a dihydronaphthalene.

8. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 50.

9. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 100.

10. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor is a compound having the formula



wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is O, S or NR^a;

R^a is alkyl;

R¹ is selected from the group consisting of H and aryl;

10 R² is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R³ is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

15 each R⁴ is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamin, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, 20 hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or R⁴ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

11. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor is (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

12. The method of claim 7 wherein the potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride, 5 iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide, nateglinide, repaglinide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

13. A method of treating pain, inflammation or an inflammation mediated disorder, the method comprising:

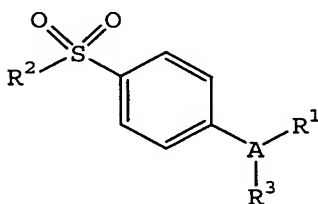
(a) diagnosing a subject in need of treatment for pain, inflammation or an inflammation mediated disorder; and

5 (b) administering to the subject a potassium ion channel modulator or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a
10 tricyclic compound, the tricyclic compound containing a benzenesulfonamide or methylsulfonylbenzene moiety.

14. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC₅₀ to COX-2 IC₅₀ not less than about 50.

15. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC₅₀ to COX-2 IC₅₀ not less than about 100.

16. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor is a compound of the formula:



5 wherein:

A is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R¹ is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R¹ is optionally substituted at a substitutable position
10 with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R² is selected from the group consisting of methyl and amino; and

R³ is selected from the group consisting of H, halo, alkyl, alkenyl,
15 alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio,

alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxyalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxyalkylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N- arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-aryl amino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-aryl amino, aminoalkyl, alkylaminoalkyl, N-aryl aminoalkyl, N-aralkyl aminoalkyl, N-alkyl-N-aralkyl aminoalkyl, N-alkyl-N-aryl aminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-aryl aminosulfonyl, arylsulfonyl, and N-alkyl-N-aryl aminosulfonyl.

17. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, parecoxib, deracoxib, rofecoxib, etoricoxib, and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

18. The method of claim 13 wherein the potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride, iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide, nateglinide, repaglinide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

19. A method of treating pain, inflammation or an inflammation mediated disorder, the method comprising:

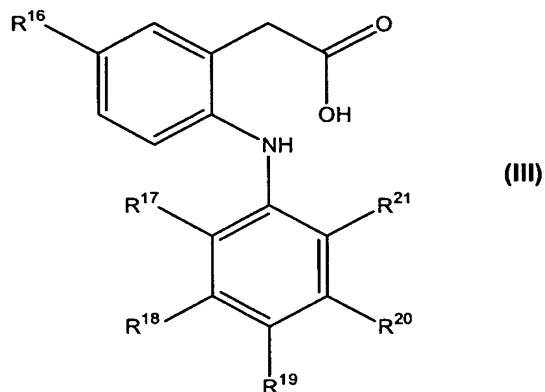
(a) diagnosing a subject in need of treatment for pain, inflammation or an inflammation mediated disorder; and

(b) administering to the subject a potassium ion channel modulator or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a phenyl acetic acid compound.

10 20. The method of claim 19 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC₅₀ to COX-2 IC₅₀ not less than about 50.

 21. The method of claim 19 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC₅₀ to COX-2 IC₅₀ not less than about 100.

 22. The method of claim 19 wherein the cyclooxygenase-2 selective inhibitor is a compound having the formula:



wherein:

 R¹⁶ is methyl or ethyl;

5 R¹⁷ is chloro or fluoro;

 R¹⁸ is hydrogen or fluoro;

 R¹⁹ is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

 R²⁰ is hydrogen or fluoro; and

10 R²¹ is chloro, fluoro, trifluoromethyl or methyl; and

 provided that each of R¹⁷, R¹⁸, R¹⁹ and R²⁰ is not fluoro when R¹⁶ is ethyl and R¹⁹ is H.

 23. The method of claim 22

wherein:

 R¹⁶ is ethyl;

 R¹⁷ and R¹⁹ are chloro;

5 R¹⁸ and R²⁰ are hydrogen; and

R²¹ is methyl.

24. The method of claim 19 wherein the potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride,
5 iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide, nategliniide, repagliniide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

25. A method of treating pain, inflammation or an inflammation mediated disorder, the method comprising:

(a) diagnosing a subject in need of treatment for pain, inflammation or an inflammation mediated disorder; and

5 (b) administering to the subject a cyclooxygenase-2 selective inhibitor selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, parecoxib, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid; and

10 a potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride, iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide,
15 nategliniide, repagliniide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

26. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is celecoxib.

27. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is deracoxib.

28. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is valdecoxib.

29. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is rofecoxib.
30. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is etoricoxib.
31. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is parecoxib.
32. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.
33. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.
34. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is lumiracoxib.
35. The method of claim 1 wherein the inflammation mediated disorder is arthritis.
36. The method of claim 1 wherein the inflammation mediated disorder is pain.
37. The method of claim 1 wherein the inflammation mediated disorder is a gastrointestinal disorder.
38. The method of claim 37 wherein the gastrointestinal disorder is selected from the group consisting of inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.